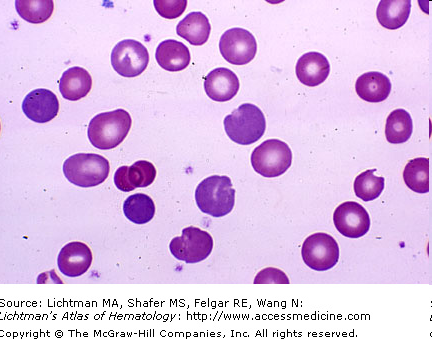
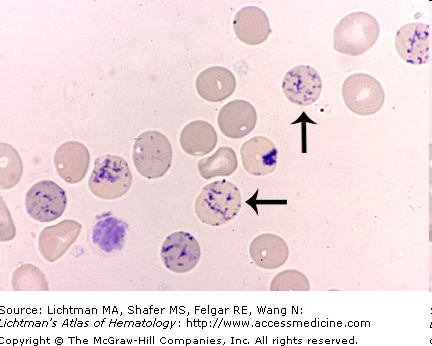
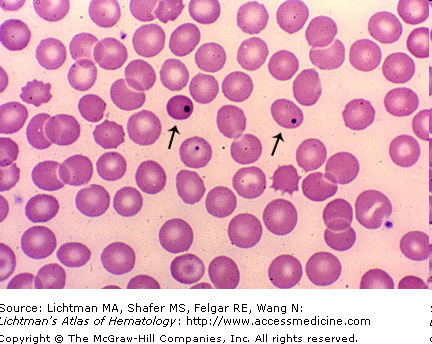
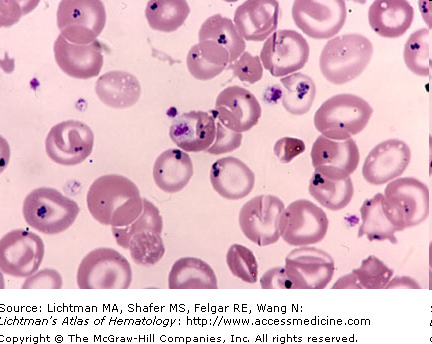
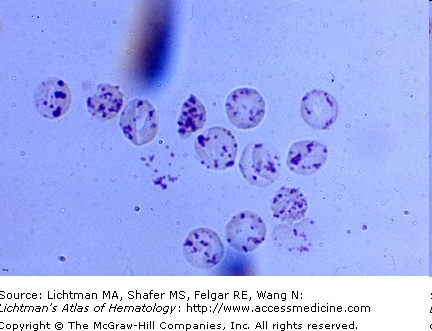
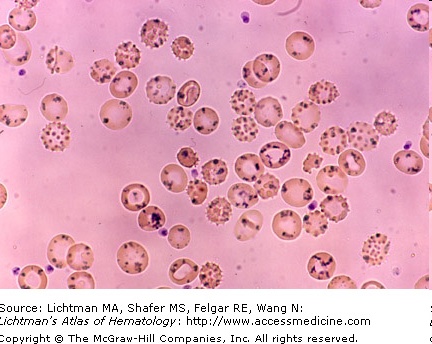
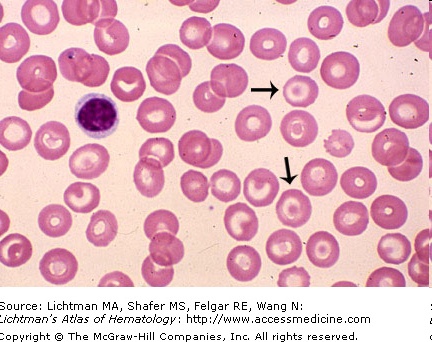
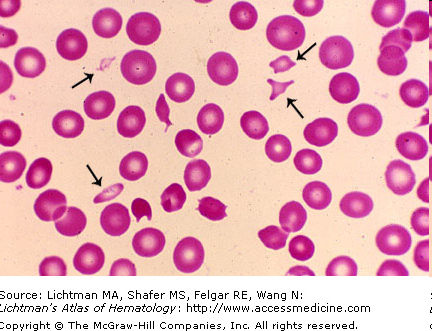
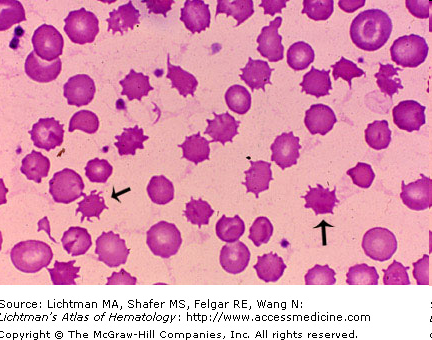
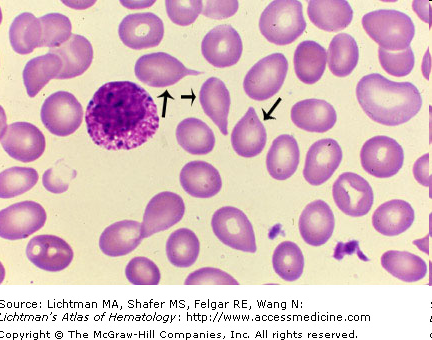
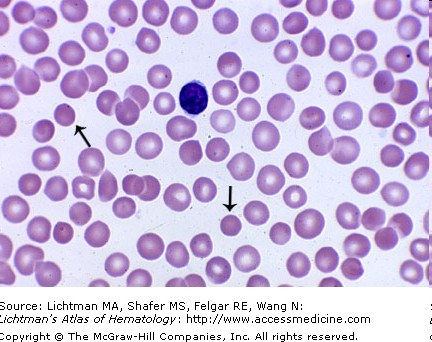
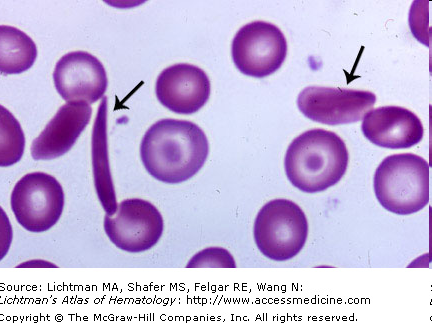
**EMBRYOGENESIS**

* 1st trimester blood production is in yolk sac and is intravascular w/ nRBC’s & Hb w/ zeta chains instead of α
* 2nd trimester blood production is in the liver and is extravascular w/ non-nRBC, and **HbF (α2 γ2)**
* 3rd trimester blood production is in bone marrow and is extravascular w/ HbA (α­2β2)
* At birth 50-50 HbF-HbA
* At 6 months Hb hould be normal adult levels (96% HbA— this includes 5% HbA1c; and 3% Hb A2 (α2δ2)
* Hematopoiesis is in the axial skeleton!
* Growth Factors
  + Stem cells-SCF (c-KIT ligand), Flt3-ligand
  + Granulocytes—GM-CSF
  + Eosinophils—IL-5
  + Monocytes—M-CSF
  + Erythrocytes—erythropoietin (used therapeutically)
  + Megakaryocytes/ platelets—thrombopoietin
  + B cells—Flt3L
  + T-cells—IL-7
  + NK cells—IL-15

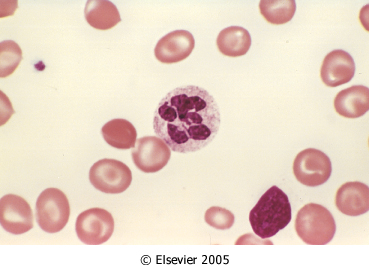
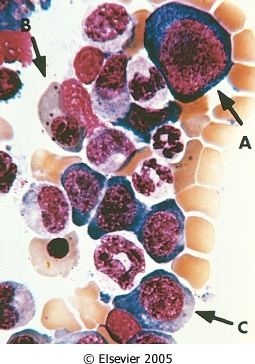
**RBC INCLUSIONS AND SHAPES**

* Anisocytosis= difference in RBC size
* Poikilocytosis = difference in RBC shape
* Calculated indices
  + MCV—mean corpuscular volume = Hct/RBC
    - Normal 80-100
    - Macrocytic >100
    - Microcytic <75
  + MCH—mean corpuscular hemoglobin = Hgb/RBC
  + MCHC—mean corpuscular hemoglobin concentration = MCH/MCV
    - How much Hgb is in red cell
    - >36 –hyperchromic (commonly seen w/ spherocytes)
    - < 32 hypochromic (commonly seen in iron def)
* RBC maturation
  + nRBC🡪 basophilic (blue, no Hgb)🡪 polychromatiphilic (pink, little Hgb) 🡪 orothochromic (red, lots of Hgb)
  + t1/2 life is 120 days and then splenic destruction and recycling of iron
  + Anemia leads to tissue hypoxia🡪 ↑ erythropoietin from kidney JG cells
* Clinical Sx of Anemia
  + Fatigue, weakness, no energy
  + Pale skin
  + Hypoxic injury: fatty change in liver, myocardium, kidney changes
  + Severe results: angina pectoris or MI, shock , renal failure etc.
* Severity of anemia
  + Hgb 10-12—MILD
  + Hgb 8—10—MODERATE
  + Hgb <8—SEVERE
  + Symptoms play a more important role in deciding how to treat b/c some ppl have a lower baseline
* **Shapes and Inclusions**
  + **Polychromasia** = young RBC w/ bluish cytoplasm
    - 
  + **Reticulocyte stain \*Special Stain= ribosomes/RNA**
    - ****
  + **Howell-Jolly body = DNA**
    - Hemolytic anemia
    - Megaloblastic anemia
    - Splenectomy
    - ****
  + **Pappenheimer bodies = iron**
    - Many inclusions close together
    - Hemolytic anemia
    - Thalessemia
    - Splenectomy—b/c this takes out RBCs w/ abnormal inclusion
    - 
  + **Basophilic Stippling = RNA**
    - Dots that are uniform w/in RBC
    - Pathological ppt of ribosomes
    - Thalessemias
    - Lead poisoning (course)
    - ****
  + **Heinz Bodies = denatured hemoglobin (Hgb inclusions) \*SPECIAL STAIN**
    - Unstable Hgb’s
    - Thalassemia
    - Enzyme deficiency (G-6-PD def.)
    - 
  + **Hemoglobin H = denatured hemoglobin \*\*SPECIAL STAIN**
    - Looks like a golf ball
    - Seen in thalassemias
    - 
  + **Target Cells**
    - Macrocytic= liver dz
    - Normocytic = Hgb C dz
    - Microcytic = thalassemia
    - 
  + **Schistocytes (fragments)**
    - Microangiopathic hemolytic anemia (TTP, DIC, malignant HTN, mechanical heart valve)
    - 
  + **Acanthocytes (irregular spikes)**
    - Liver dz
    - Abetalipoproteinemia
    - 
  + **Tear drops**
    - Thalassemias
    - Myelofibrosis
    - 
  + **Echinocytes (spiny sea urchin/burr cells)**
    - \*think kidney dz
    - Uremia
    - Pyruvate kinase def
    - 
  + **Spherocytes (solid sphere, no pallor)**
    - Hereditary hemolytic anemia
    - Immune hemolytic anemia
    - Transfusion reaction
    - 
  + **Sickly Cell**
    - SS, SC, S-thalassemia (NOT seen in AS)
    - 

**ANEMIA OVERVIEW**

* Fatigue, weakness, no energy, SOB, dizziness, headache, chest pain
* Pale skin, maybe tachycardia ro arrhythmia
* Dx: do a CBC!—what is the Hgb and what is the MCV?
  + MCV—mean corpuscular volume = Hct/RBC
    - Microcytic <75
      * **Iron Deficiency**
      * **Chronic Blood loss**
      * **Thalassemia**
      * **Sideroblastic anemia**
    - Normocytic 80-100
      * **Acute blood loss**
      * **Chronic dz**
      * **Myelophthisic (BM replacement) anemia**
      * **Aplastic (BM failure) anemia**
      * **Hemolytic anemia**
    - Macrocytic >100
      * **B12 deficiency**
      * **Folate deficiency**
      * **Alcohol and liver dz**
      * **Hypothyroidism**
  + MCHC—mean corpuscular hemoglobin concentration = MCH/MCV
    - How much Hgb is in red cell
    - >36 –hyperchromic (commonly seen w/ spherocytes)
    - < 32 hypochromic (commonly seen in iron def)

**MACROCYTIC/MEGALOBLASTIC ANEMIA** (-cyte = peripheral blood; blast= in BM)

* **B12 deficiency**
  + Reactions that need B12
    - Homocysteine 🡪 methionine
      * Necessary for DNA synthesis (dUMP🡪 dTMP)
        + So B12 def. will cause ↓ DNA synth
      * N-methyl-H4-folate trap
      * Homocysteinemia—may lead to accelerated atherosclerosis
    - MethylmalonylcoA🡪 succinylCoA
      * Methylmalonic acid (good test)
      * Methylmalonic academia may lead to abn lipids in neurons
      * Succinyl CoA is important precursor to hemoglobin synthesis
  + Outcome: ↓ DNA synth, nuclear/cytoplasmic asynchrony, intramedullary destruction
  + Peripheral blood “big bands” and **hypersegmented neutrophils!!!! >5 lobes (normally has 2-5)**
    - **Also should think of folate def.**
    - 
  + Macrocytic b/c cells keep getting bigger and bigger w/o signal to divide from DNA and then they are destroyed
  + Normal B12 abs
    - Diet!
    - Stomach—need IF
    - **Terminal ileum absorption** (abs. B12-IF complex)
    - Liver storage (supply lasts years so it takes years to become B12 def)
  + Causes
    - Poor diet
    - ↑ needs (pregnancy, malignancy, hyperthyroidism)
    - Stomach problems (loss of IF)
      * Atrophic gastritis or pernicious anemia
      * Gastrectomy
    - Small intestine problems
      * Bacterial overgrowth (blind loop sx)
      * Fish tapeworm (diphyllobothrium latum)
    - Terminal ileum problems (loss of abs)
      * Crohn’s dz
      * Resection
  + Sx’s will improve w/ folate but neurological complications are not improved
  + When you do BM aspiration will see:
    - 
  + **Pernicious Anemia (severe problem)**
    - Autoimmune cause
      * Abs to parietal cells which make IF (most common) OR
      * Abs to IF itself
      * Order test to look for both Ab’s to differentiate
    - Results in
      * **atrophic gastritis**, no chief cells, intestinal metaplasia and ↑ risk for gastric cancer.
      * **SACD (subacute combined degeneration of the spinal cord)**—demyelination of posterior and lateral columns🡪 leg paresthesias, sensory ataxia, spastic paresis
* **Folate Deficiency** 
  + Folate reactions are one carbon transfers necessary for DNA synthesis
  + Megaloblastic marrow and hypersegmented PMNs (also seen in B12 def)
  + Causes
    - Poor diet (alcoholics) or malabs
    - ↑ need 9Pregnancy, malignancy)
    - ↑ loss (dialysis patient)
    - Folic acid antagonists (methotrexate)
  + ↑ FIGlu excretion, homocysteinemia
  + **Jejunum abs**
  + Supply lasts only months (takes less time to become deficient)
  + NO neurological complications
* Work up for Macrocytic Anemia
  + Order both serum B12 and serum folate
    - If B12 order anti-IF and anti-parietal cell Abs
    - If pernicious anemia need to tx w/ B12 injections

**MICROCYTIC ANEMIA**

* **Iron Deficiency**
  + MOST COMMON nutritionsal disorder in the WORLD
  + **Duodenal absorption**
  + Cause
    - Poor diet, impaired abs, excess demand,
    - CHRONIC BLOOD LOSS
      * GI or GU tumors, ulcers, angiodysplasia, esophageal varices, menstruation
      * \*\*IRON DEF IS GI BLOOD LOSS INCLUDING CANCER UNTIL PROVEN OTHERWISE\
        + if you tx w/ iron your feeding that tumor!!!
        + Do a colonoscopy
  + Signs and Sx
    - Koilonychias—spoon nails
    - Alopecia
    - PICA
    - Rarely Plummer-Vinson sx (microcytic hypochromic anemia, atrophic glossitis, esophageal webs)
  + ↑ hepcidin inhibits absorption of iron in the duodenum
    - hepcidin also suppresses iron release from storage macrophages (anemia of chronic dz)
  + Stages
    - ↓ BM iron stores (ferritin, an iron/protein complex, and hemosiderin (this stains w/ Prussian blue)
    - ↓ serum ferritin
      * + not good to dx b/c it is an acute phase reactant
    - ↓ serum iron and ↑ TIBC (total iron binding capacity)
    - Microcytic hypochromic anemia
      * ****
* **Thalessemia Syndromes**
  + Genetic cause
  + ↓ hemoglobin A chain synthesis
  + common in Mediterranean, Africa, India, SEA
  + gives some malaria protection
  + Alpha thalassemia
    - ↓ alpha chains (results in too many unpaired beta chains)
    - 4 genes (two on each chromosome 16)
    - Mechanism = gene deletion
      * + Lose 1 gene, α-thal silent carrier
        + Lose 2 genes, α-thal trait,

slight anemia

(α/α, -/-) common in Asia

(α/-, α/-) common in Africa

* + - * + Lose 3 genes, HbH disease

live to adulthood

moderate anemia

HbH = β4 tetramer

poor oxygen delivery

**Heinz bodies** can be seen with brilliant cresyl blue

* + - * Lose 4 genes, Hb Barts = γ4 tetramer
        + Fatal
        + hydrops fetalis, die in utero or shortly after birth
  + Beta thalassemia
    - ↓ beta chains (too many unpaired alpha chains)
    - 2 beta genes (chromosome 11)
    - Anemia starts ~ 6 months of age with switch from HbF to HbA
    - Mechanism = gene mutation
      * + **Genotypes**

**β β** (normal genotype)

β+ (decreased synthesis)

β0 (no synthesis)

* + - * + **β thal major**: both genes bad, severe anemia, transfusion dependent, increased HbF
        + **β thal minor**: usually one bad gene, mild anemia, increased HbA2

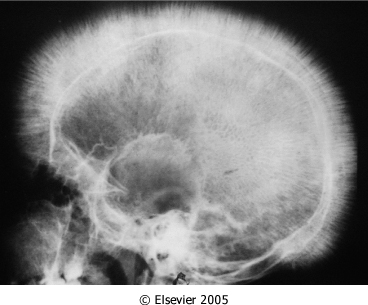
protects against falciparum malaria (also, sickle trait, G-6-PD deficiency)

if less HgA then ↑ HgF or ↑ HgA2

* + - * + **β thal intermedia**: moderate anemia
  + Result for both:
    - unbalanced hemoglobin chains, the excess chain precipitates on and damages the RBC membrane resulting in intramedullary destruction (ineffective erythropoiesis)
  + Peripheral blood microcytic will see anemia, bizarre poikilocytosis with **target cells**
  + Bone marrow expansion with **skeletal deformity**—red marrow expands @ expense of bone cortex!
  + Can cause hepcidin suppression🡪 ↑ Fe abs 🡪 Secondary hemochromatosis 🡪 affects liver (cirrhosis), heart (CHF) and pancreas (bronze diabetes)
  + Dx and Complications
    - Family hx
    - peripheral smear🡪microcytic RBCs, many **target cells**
    - Hb electrophoresis
      * + ↑ HbF or A2 seen in β-thal.

Can’t make up for no α chains!

* + - * + Hb H or Hb Barts may be seen in α-thal.
    - Gene analysis can be done in utero
    - Complications of severe disease
      * + Bone marrow expansion and skeletal deformity



hair on end xray

can also be seen in dz’s that cause ↑ BM hematopoiesis like sickle cell anemia

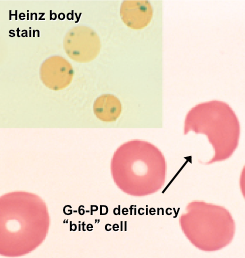
* + - * + Pigmented gallstones (may lead to pancreatitis or gallbladder carcinoma)
        + Hepatosplenomegaly
        + Secondary hemochromatosis (iron overload (low hepcidin) and multiple transfusions, leads to heart failure, bronze diabetes, cirrhosis)

|  |  |  |  |
| --- | --- | --- | --- |
| **Anemia** | **Serum Fe** | **TIBC** | **BM Fe** |
| **Fe deficiency** | **↓** | **↑** | **zero** |
| **Sideroblastic anemia** | **↑** | **↓** | **Increased, with ringed sideroblasts** |
| **Thalassemia** | **normal** | **normal** | **Increased** |
| **Chronic disease** | **↓** | **↓** | **increased** |

**NORMOCYTIC ANEMIAS**

* 5 categories
* Acute blood loss, chronic disease, BM replacement, BM failure, hemolytic
* Acute blood loss
* Anemia of chronic disease (Hgb stabilizes ~8)
  + chronic infections, immune diseases, malignancies = very common
  + ↑ serum ferritin, ↓ serum Fe, ↓ TIBC, BM Fe present.
  + Etiology – chronic inflammation and IL-6 leads to elevated hepcidin🡪 iron cannot be transported or used properly in the marrow so can’t make Hgb🡪 anemia
* Myelophthisic anemia
  + BM replacement by tumor (prostate, breast), fibrosis, granulomas, etc
* Aplastic Anemia
  + pancytopenia (↓ WBC, ↓ platelet, ↓ Hgb) with anemia, bleeding, infections, **no spleen enlargement**
  + In BM aspirate will see lots of fat and not a lot of cellularity (normal BM is ~50% fat)
  + most are acquired
    - 65% idiopathic
    - chemoRx or radiation
    - viruses (hepatitis, CMV, EBV)
    - drugs (e.g. chloramphenicol - reversible dose-related, irreversible idiosyncratic)
  + rarely inherited
    - Fanconi anemia
      * Rare autosomal recessive
      * Bad DNA repair mechanisms, chromosome gaps
      * Pancytopenia and **congenital abnormalities**
      * Hypoplasia of kidney, spleen, absent radii or thumb (absent radii also seen in TAR babies – thrombocytopenia with absent radii)
    - Estren-Dameshek anemia
      * No associated congenital abnormalities
    - pure red cell aplasia
      * Seen with thymoma, parvovirus B19, others
    - teleromase defects: stem cell depletion
* Hemolytic Anemias
  + Intrinsic RBC defects
    - Membrane (hereditary spherocytosis, PNH-acquired)
    - Enzymes (glucose-6-phosphate dehydrogenase deficiency)
    - Hgb structure (sickle cell anemia)
  + Extrinsic cause of RBC destruction
    - Antibodies (Coombs+ hemolytic anemia)
    - Mechanical (e.g. heart valves)
    - Microangiopathic hemolytic anemia
  + Peripheral blood smear, for morphology 🡪spherocytes, schistocytes
    - Schistocytes also in DIC, TTP, and HUS
  + Intravascular destruction
    - Anemia with hemoglobinemia, elevated LDH, ↓ haptoglobin (picks up free Hgb), hemoglobinuria, hemosiderinuria, unconjugated hyperbilirubinemia (jaundice), pigmented gallstones
    - (but generally not splenomegaly)
  + Extravascular destruction
    - Anemia with splenomegaly, jaundice (unconjugated), pigmented gallstones
    - (but generally not hemoglobinemia, not hemoglobinuria, not hemosiderinuria)

**HEMOLYTIC ANEMIAS: INTRINSIC RBC DEFECTS**

* **Hereditary Spherocytosis** 
  + Inherited, autosomal dominant (+ family history)
  + Northern European populations, 1 in 5000 persons
  + **Spectrin or ankyrin deficiency**
  + membrane loss leads to spherocytes (decreased surface/volume)
    - same amount of Hgb being packing into a smaller space
  + RBCs destroyed in spleen
  + Sx: Anemia, jaundice, splenomegaly, gallstones
  + Will see Spherocytes
  + Coombs negative—no Abs
  + ↑ osmotic fragility (in a hypotonic solution)
    - not much wiggle room in RBC structure
  + Hemolytic crisis
    - Hemolyze a lot of RBC at once🡪 may be ppt by infections, drugs, anything that stresses the RBC’s
    - Can get aplastic crisis with Parvovirus B19
  + Rx: splenectomy can lessen the anemia, but spherocytes still present
* **PNH Paroxysmal Nocturnal Hemoglobinuria**
  + Rare, acquired clonal stem cell defect (premalignant)
  + Clinical presentation uncommonly “PNH,” mostly pancytopenia or clotting (can be fatal)
  + Acquired defect is PIGA gene mutation leading to deficiency of glycosylphosphatidylinositol anchor protein
    - Results in lack of membrane CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis), leading to Complement- mediated intravascular lysis of ALL cells (**WBC, RBC, platelets = pancytopenia**)
  + Will see tea colored urine
  + Chronic hemolysis 🡪anemia, jaundice, gallstones
  + Venous thrombosis due to platelet dysfunction (hepatic, portal or cerebral veins)—50% fatal if cerebral
  + Clinical triad
    - hemolysis/pancytopenia/thrombosis
  + Dx test is flow cytometry to look for CD55/CD59
  + Confirmatory test: Ham test (acid hemolysis)
  + 10 yr survival
  + ↑ risk of acute leukemia and aplastic anemia
* **Enzyme Defects: G-6-PD ↓**
  + Glucose-6-phosphate dehydrogenase deficiency
    - in the HMP shunt
    - enzyme deficiency leads to ↓ NADPH, then ↓ reduced glutathione, resulting in oxidative injury to RBCs
  + Sex-linked, males, splenic destruction
  + Hemolytic episodes associated with drugs (Primaquine) or infection; also, fava beans (favism)
  + May protect against falciparum malaria
  + 2 patterns of hemolysis
    - G6PD-- enzyme defect
    - Mediterranean enzyme defect
  + G6PD—
    - enzyme normal amount and function, but decays faster than normal
    - Hemolysis of **older** RBCs, self-limited, less severe, seen in 10% of African Americans
  + Mediterranean
    - enzyme insufficient quantity or defective
    - Severe hemolysis of **all** RBCs
  + On peripheral blood smear
    - Intravascular hemolytic anemia
    - “bite” cells in blood
    - Heinz bodies (crystal violet stain)
    - extravascular hemolysis
    - 
  + Dx: quantitate the enzyme levels , but NOT during a hemolytic episode
* **Hb Defect: Sickle Cell Anemia**
  + Sickle cell anemia: β chain **#6 glutamate replaced by valine**
  + AS sickle trait (want to know for passing it on to kids)
    - 1 normal β chain
    - 1 sickle β chain
    - rarely sickle
    - protects against falciparum malaria
  + Sickling diseases – cause microvascular occlusion
    - Sickle cells can revert back to normal shape but after enough times it gets permanently stickled. Once sickled they RBC’s get sticky🡪 get stuck in microvasculature🡪 cause occlusion 🡪 free Hg scavenges NO🡪 ↓ in NO 🡪 no dilation of arterioles 🡪 anoxic tissue
    - SS sickle cell anemia
      * both β chains sickle type
      * most severe disease
      * SS complications
        + Sequestration crisis: kids only, acute splenomegaly and hypotension, possible death
        + Vaso-occlusive crisis (painful crisis)

Spleen- autosplenectomy by teenage yrs, increased infection with encapsulated bacteria, e.g. Strep. pneumoniae

Hand-foot syndrome (dactylitis; esp. in kids)

Sickling in hands and feet🡪 anoxia in these areas

Femoral head- aseptic necrosis

Lungs- acute chest syndrome, cor pulmonale

Brain- stroke

Skin- ulcers

Penis- priapism

Aplastic crisis- many times related to Parvovirus B19

Hemolytic crisis

Megaloblastic crisis

* + - * + Others

Bone abrnomalilites (crewcut skull x-ray)

Pigmented gallstones

Secondary hemochromatosis (iron overload 🡪 bronze DM)

Renal papillary necrosis

Drug addiction (narcotics)

* + - SC disease
      * + one HbS β chain & one HbC β chain (#6 glutamate to lysine)
        + milder disease
        + Will see sickles and target cells on peripheral smear
        + Electrophoresis will show HbS and HbC and MCV will be normocytic
        + HbC dz

Many target cells and HbC crystal

HbC trait is relatively benign but homozygous CC has mild hemolytic anemia and splenomegaly

Only HbSC dz are there severe symptoms

* + - S-thalassemia
      * + 1 sickle β chain, 1 β chain thalassemia type
        + milder disease
        + Will see sickles and microcytosis
  + Causes of Sickling and Dx
    - Sickling caused by low O2 tension, low pH (acidosis) or dehydration; infection (causes sticky RBCs)
    - Sickling is initially reversible, but repeated sickling results in a permanently sickled cell
    - HbF can have a protective effect
      * So newborns don’t sickle until about 6 mos.
        + b/c at 6 months HbF is ~1%
      * Hydroxyurea can increase HbF
    - Dx: sickle cells on blood smear, Hb electrophoresis (prenatal by DNA analysis)
      * Electrophoresis will tell if they have HbA (in SS only have HbS)

**HEMOLYTIC ANEMIAS: EXTRINSIC RBC DEFECT**

* **Coombs+ Hemolytic Anemias**
  + Antibody-mediated; autoimmune hemolytic anemias (alloimmune hemolysis is a transfusion reaction)
    - Coombs test detects Ab to RBCs
    - Direct Coombs = Ab (or C`) directly on RBC
    - Indirect Coombs = Ab in the serum
  + 3 types of Abs
    - **Warm autoimmune Hemolytic Anemia**
      * Ab reactive at 37o (Room temp) , usually IgG, does not fix Complement
      * Spherocytes form as Ab removed in spleen, splenomegaly (extravascular hemolysis)
        + (Intravascular hemolysis occurs if C` is fixed)
      * Causes
        + Idiopathic 50%
        + Lymphoma (chronic lymphocytic leukemia)
        + Autoimmune diseases (SLE)
        + Drugs (first 2 models require drug for hemolysis)

Hapten model (penicillin)- Ab against drug on the RBC membrane

Immune complex model (quinidine)- Ab against drug/protein complex on RBC membrane

AutoAb model (Aldomet)- Ab against drug, then attacks RBC separately (drug does not need to be present for continued hemolysis)

* + - **Cold agglutinins (cold auto-Ab)**
      * Antibody active at 0-4 Co, so this is mostly a laboratory artifact when cooled blood is run thru the machine (not clinically significant)
      * IgM binds to RBC in cooled body parts, may fix C`, but IgM and C` release in warmer areas, so hemolysis is rare; may cause Raynaud phenomenon (Robbins p. 518)
        + (cryoglobulinemia is a different autoimmune disease: Abs cause Raynauds, but Abs are NOT directed against RBCs)
      * Acute cold agglutinin is a good clue to underlying disease
        + Mycoplasma pneumonia (anti-I specificity)—big I carb
        + Infectious mononucleosis (anti-i specificity)—little I carb
      * CBC clues to Dx: low RBC count, greatly elevated indices when blood is run at room temp; warm tube of blood to 37° and RBC count comes up to normal and indices come down to normal
    - **Cold hemolysins**
      * Clinically significant b/c active at 28-30 o
      * Historically called Donath-Landsteiner Ab, originally discovered in syphilis patients
        + Now see most commonly w/ viruses
      * Patient may have hemoglobinuria, so this is also called **PCH paroxysmal cold hemoglobinuria (don't confuse w/ PNH)**
      * Now rare, mostly seen in viral infections
      * Usually IgG binds in cooled parts (fingers, toes), fixes C`, and causes significant intravascular hemolysis when RBC circulates to warmer area where C` activates
      * **Anti-P specificity**
  + **Dx Possibilities for Schistocytes**
    - Prosthetic heart valve—as RBC goes through valve it gets chopped up
    - march hemoglobinuria (a long walk, not the month!!!)—sheer forces in the heel break up RBC’s
    - Severe burns (red cells explode and fragment)
    - **DIC**
    - **HUS**
    - **TTP**
    - Malignant hypertension
    - Vasculitis (e.g. SLE systemic lupus with vasculitis)
* **Mechanical Hemolysis**
  + Blood smear shows schistocytes
  + One example: caused by shear force as RBCs go thru prosthetic heart valves
  + Another variant is “march” hemoglobinuria
    - On long marches, the shear force of pounding the heel against pavement causes hemolysis with resulting hemoglobinuria
  + Other examples of “extrinsic” hemolysis include severe burns, infection (malaria, babesiosis), chemicals (lead)
* **Microangiopathic Hemolytic Anemias**
  + **DIC**
    - Not a primary disease, but a complication of other medical problems
      * Many predisposing causes: sepsis, obstetric complications, major trauma, severe burns, malignant tumors, esp. mucinous adenocarcinomas and acute myelocytic anemia with t(15;17)
    - 2 major trigger mechanisms
      * Release of tissue factor or thromboplastic substances
      * Widespread endothelial injury
    - Widespread fibrin thrombi in the microcirculation, results in hypoxia and organ dysfunction, esp. brain/kidneys/heart/lungs; schistocytes from RBC fragmentation
    - Rapid consumption of coagulation factors and platelets (consumption coagulopathy) resulting in serious hemorrhage risk (hemorrhagic diathesis)
    - ↑ PT and PTT, ↓ fibrinogen, ↑ fibrin split products
    - Rx: treat the cause
  + **HUS**
    - HUS hemolytic uremic syndrome
    - Most common etiology, gut *E. coli* O157: H7 production of a shiga-like toxin which binds to glomerular endothelial cells, platelet thrombi mostly in kidney
    - Clinical presentation- kid with bloody diarrhea, after eating undercooked meat or visiting a petting zoo
    - Dx triad microangiopathic hemolytic anemia (schistocytes), thrombocytopenia, renal failure
      * Kidney endothelium is damaged
    - PT/PTT usually normal
    - Rx supportive, dialysis as necessary, do NOT give antimicrobials or antidiarrheals
  + TTP
    - Mainly a dz of adults
    - Dx pentad: like HUS plus fever and neurologic signs (confusion, seizure, etc.); normal PT/PTT; widespread thrombi, any organ; a medical emergency
    - Most common etiology--autoimmune disease, antibodies to von Willebrand cleaving enzyme (ADAMTS 13 or vWF metalloprotease)
    - clopidogrel (Plavix) is a frequent etiology.
    - Enzyme deficiency causes abnormal large vW multimers in the small vessels, initiating platelet thromboses
    - Rx plasma exchange with FFP helps get rid of the antibody and replace the enzyme; **do NOT give platelets they will make it worse**

**MISCELLANEOUS RBC PROBLEMS**

* **Porphyria**
  + **Abnormal hemoglobin synthesis**
  + Heme synthesis enzyme deficiency
  + Cutaneous photosensitivity, neurologic abnormalities, abdominal pains
  + Increased AmLev in all acute porphyrias with neurologic symptoms
  + Urine PBG is a good screening test during acute attacks
  + Fluorescent urine (with a black light or Wood’s lamp) is a good clue in babies
  + Porphyria cutanea tarda
    - Most common
      * 
* **Increased RBC’s**
  + **Polycythemia**
    - Reactive/relative (decreased plasma volume)
    - Associated with dehydration
    - Gaisbock stress syndrome (fat stressed out hypertensive patient)
  + **Absolute polycythemia (increased red cell mass)**
    - Primary polycythemia rubra vera (decreased EPO)
    - a chronic myeloproliferative disease; JAK 2 mutation in 90%
    - Acquired clonal stem cell disorder, elderly patients
    - RBC’s growing out of control, so EPO is low or non-detectable
    - Splenomegaly
    - Increased risk acute leukemia; burnout stage myelofibrosis of marrow
  + **Secondary polycythemia (increased EPO)**
    - Seen in lung disease/smokers (CO poisoning), heart disease
    - EPO-producing tumors: renal cell Ca, cerebellar hemangioblastoma
      * EPO comes from kidney
    - ALWAYS CHECK CO LEVELS!!